

Metoclopramide, an Increasingly Recognized Cause of Tardive Dyskinesia

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Tardive dyskinesia (TD), a hyperkinetic movement disorder causally related to dopamine receptor-blocking drug (DRBD) exposure, is a well-recognized iatrogenic disorder in adults¹ and less commonly seen in children and infants.^{2,3} Although the literature on TD mainly focuses on patients treated with DRBDs used as antipsychotics, DRBDs are also used to treat a wide array of medical, chiefly gastrointestinal, conditions.⁴⁻⁶ Although most of the drugs that cause TD are DRBDs that antagonize dopamine D₂ receptors, other classes of drugs have the potential to cause TD, including antidepressants and calcium channel blockers. The reported lifetime prevalence of TD in patients treated with traditional DRBDs has varied greatly, with an average of about 25% of exposed adults.^{1,7} Risk factors associated with the development of TD include advanced age, female gender, and, more important, total cumulative drug exposure.⁸⁻¹¹ We sought to determine which drugs most commonly cause TD in patients referred to our clinic.

MATERIALS AND METHODS

After approval by the institutional review board, a retrospective chart review of 583 charts was performed

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on patients evaluated for TD in the Parkinson's Disease and Movement Disorders Clinic at Baylor College of Medicine between 1981 and January 2006. We included all patients who met clinical criteria for TD¹²: (1) exhibited a hyperkinetic movement disorder, (2) had a documented exposure to 1 or more DRBDs for at least 3 months before the onset of symptoms, and (3) the hyperkinetic movement disorder persisted for at least 1 month after stopping the offending DRBD.¹² A total of 434 charts were used specifically for this study; 149 charts were excluded because of incorrect diagnostic coding, accidental destruction of charts, and loss to follow-up. We excluded patients with drug-induced parkinsonism.¹³ All data related to demographics (age/gender), treatment indication (psychiatric/gastrointestinal/other), phenomenology (stereotypy/dystonia/choreatic/tremor), and offending agent were captured on case report forms and transferred to a database.

RESULTS

We report data on 434 TD patients for whom we have detailed clinical information. Patients, of whom 334 were women (77.0%), had a mean age of 63.8 ± 14.8 years at their initial evaluation. Since its inception, 23 653 movement disorder patients have been evaluated at Baylor College of Medicine, 11 802 of whom were women (50.0%). There was no statistical difference in the proportion of women presenting with a psychiatric treatment indication when compared with those with a gastrointestinal disorder. The majority presented with oro-facial-lingual stereotypy (n = 198, 45.6%), dystonia (n = 165, 38.0%), or other stereotypies (n = 159, 36.6%).

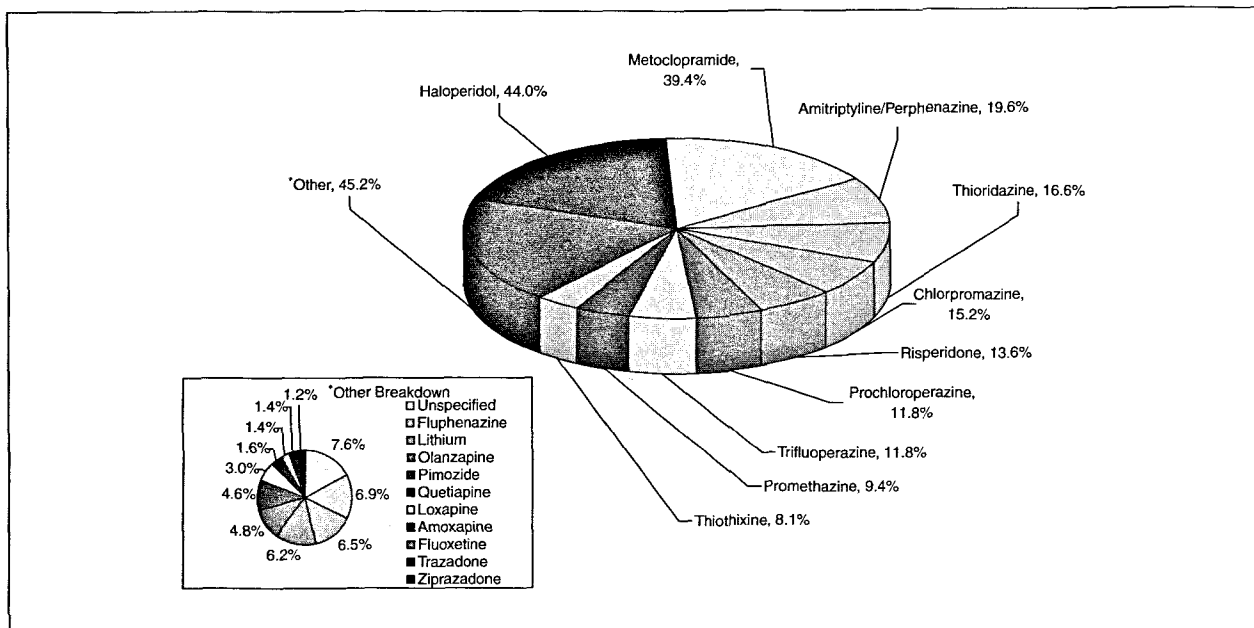


Figure 1. Medications associated with tardive dyskinesia.

Chorea ($n = 21$, 4.8%) and tics ($n = 17$, 3.9%) were less common; many patients ($n = 187$, 43.1%) presented with mixed phenomenology. Treatment indications included psychiatric (68.2%), gastrointestinal (30.0%), and other (1.8%). A specific causal DRBD was defined for 411 (94.7%) patients. The most common medications associated with the onset of TD were haloperidol ($n = 191$, 44.0%), metoclopramide ($n = 171$, 39.4%), amitriptyline/perphenazine ($n = 85$, 19.6%), and thioridazine ($n = 72$, 16.6%) (Figure 1). From 1981 to 1999, the most common cause of TD was haloperidol; however, from 2000 to 2006, metoclopramide-induced TD was more common than any other cause, accounting for 34.5% of all cases compared with 24.4% for haloperidol (Figure 2).

DISCUSSION

We reviewed 434 patients seen over the past 25 years at the Parkinson's Disease Center and Movement Disorders Clinic at the Baylor College of Medicine. Historically (1981-1999), haloperidol was the most common cause of TD in our clinic. In recent years (2000-2006), we evaluated more patients with metoclopramide-induced TD, a finding consistent with other investigators.⁵ This may simply reflect a referral bias whereby fewer patients with haloperidol-induced TD are being sent to subspecialty clinics.

Nevertheless, physicians should be aware that drugs not used to treat psychosis may still cause TD, especially if used for prolonged periods.⁵ The number of patients referred with haloperidol-induced TD has been gradually declining, whereas TD from thioridazine has dramatically decreased, probably reflecting newer pharmacologic drugs as options in the treatment of psychosis.⁷ The introduction of modern DRBDs has led to a rise in the number of patients presenting with TD related to these drugs,¹⁴⁻¹⁸ especially risperidone in our study. Dopamine receptor-blocking drugs clearly cause most cases of TD, but lesser known drugs that may indirectly block dopamine receptors in a poorly understood manner may cause this hyperkinetic disorder, such as the antidepressants fluoxetine and doxepin.^{19,20}

Most TD patients present with stereotypy, particularly oro-facial-lingual dyskinesia, the classic hyperkinesia associated with TD. Dystonia, tremor, and akathisia were also common, and nearly half displayed mixed phenomenology. In a small percentage of patients, no causative agent was discovered to explain adult-onset stereotypy. This finding may be explained in part by the relatively common occurrence of spontaneous oral dyskinesia in the edentulous elderly.^{7,21} Other, rare causes of spontaneous stereotypies include neuroacanthocytosis, cerebellar disorders, and Huntington's disease.^{22,23}

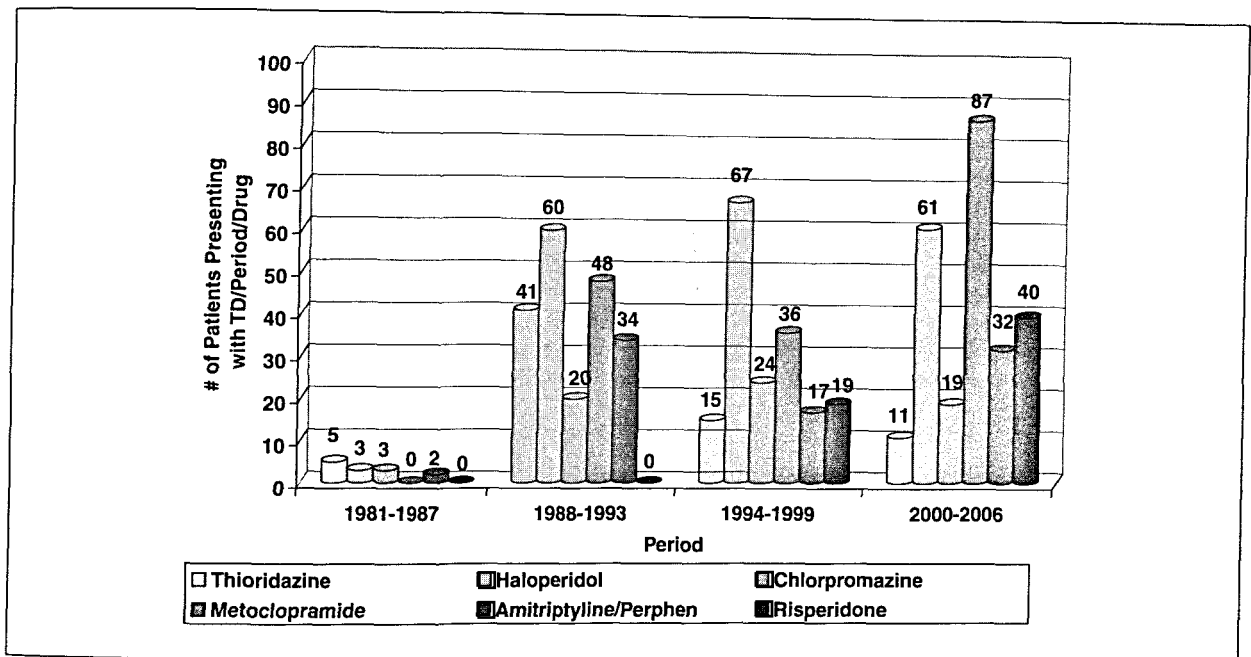


Figure 2. Temporal distribution of medications associated with tardive dyskinesia (TD).

Despite the recognition of TD more than half a century ago, the pathophysiology of this iatrogenic disorder is still not well understood.²⁴ Several lines of evidence support the involvement of dopaminergic systems in the pathogenesis of TD. Dopamine receptor-blocking drugs may cause, improve, or even worsen TD (during withdrawal). Similarly, drugs that deplete dopamine ameliorate TD; dopamine agonists may exacerbate TD. Positron emission tomography (PET) studies in humans implicate D₂ receptor upregulation.²⁵ The leading hypothesis suggests that chronic blockade of dopamine receptors leads to increased dopamine receptor sensitivity.²⁶ Although most drugs with the potential to cause TD belong to the antipsychotic family of drugs (phenothiazines, thioxanthenes, butyrophenones, etc), other medications for non-psychiatric-related problems, such as metoclopramide, antagonize dopamine receptors and may, therefore, cause TD. Given our current level of understanding of the pathophysiology, we recommend caution treating TD with DRBDs, even the so-called atypical antipsychotics, such as risperidone,²⁷ amisulpride,²⁸ quetiapine,²⁹ or aripiprazole,³⁰⁻³² as many of these drugs are not truly "atypical" and have been associated with TD.^{18,33-35} It is not known why female patients are at a greater risk to develop TD, but it has been reported in several

studies.³⁶⁻³⁸ Some investigators theorize that estrogen levels modulate dopamine receptors.³⁹

Since obtaining Food and Drug Administration (FDA) approval in 1979, metoclopramide has become the most widely used agent for gastrointestinal motility disorders, particularly after the withdrawal of cisapride from the US market in 2000.⁵ Metoclopramide blocks D₁ and D₂ receptors centrally in the chemoreceptor trigger zone (antiemetic) and peripherally in myenteric neurons (prokinetic).⁶ Other pharmacologic properties include 5-HT₃ receptor antagonism, 5-HT₄ receptor potentiation, and sensitization of muscarinic receptors.⁵ Metoclopramide treats several gastrointestinal problems, including nausea, vomiting, gastroparesis, and gastroesophageal reflux disease. Although the FDA approved metoclopramide only for the short-term treatment of adults with diabetic gastroparesis, this particular disorder is chronic and necessitates continuous treatment in most patients. In 1 study of elderly patients, nearly a third reported taking metoclopramide for more than 1 year.⁴⁰ Furthermore, metoclopramide is sometimes continued despite the emergence of TD.⁴¹ One study found that TD emerges on average 12 months after the initiation of metoclopramide, and the treatment was continued for an average of 6 months after involuntary movements started.⁴² To further complicate

matters, many patients with TD are often not aware of their involuntary movements.⁴³

Several other studies have reported that metoclopramide causes TD in adults,^{12,44} and some suggest metoclopramide to be the most common cause of TD.^{5,45} A previous review of 131 patients with drug-induced movement disorders at our institution found metoclopramide to be the causative agent in 12% (n = 16) of patients, all of whom had been exposed to 20 to 40 mg/day.⁴² Another study of metoclopramide-treated adult patients reported that 29% (n = 15) met criteria for TD, compared with 17.6% (n = 9) of metoclopramide nonusers (*P* = .08).⁴¹ We believe that metoclopramide is also an important cause of TD in children and may be underrecognized; only 2 children with metoclopramide-induced TD are reported in the literature.^{3,46}

In long-term studies, the incidence of TD due to first-generation antipsychotics was reported to be 5% per year in adults and 25% to 30% in elderly patients, whereas the incidence of TD due to second-generation antipsychotics was 0% in children and 6.8% in the mixed adult and elderly population.^{15,47} In adult patients, studies suggest that the risk of TD with modern DRBDs is 4-fold less when compared with traditional DRBDs.^{15,16} Although atypical antipsychotics may be better alternative medications with less risk of causing TD, the risk of TD may increase with chronic use of these drugs, similar to the neuroleptics. In a recent review of TD epidemiology, Tarsy and Baldessarini⁷ suggest that the increased use of modern neuroleptics in clinical practice may paradoxically increase the total number of patients with TD. Based on recent reports, the following rank of lowest to highest risk of TD has been suggested: clozapine < quetiapine < aripiprazole < olanzapine = ziprasidone < risperidone.^{14,15,48} The major pharmacologic differences with the modern DRBDs that may explain the lower risk of TD are lower D₂ receptor affinity, rapid receptor dissociation, and potent 5-HT_{2A} receptor antagonism. Despite this advantage, a large placebo-controlled study concluded that adverse effects of modern DRBDs (risperidone, olanzapine, quetiapine) offset the benefit provided to Alzheimer's disease with psychosis, agitation, and aggressive behavior.⁴⁹

Avoiding DRBDs is the best approach to minimizing the development of TD, particularly in a high-risk population, such as elderly women or patients with psychiatric comorbidities. In addition, attention should focus on avoiding prolonged treatment duration and high DRBD dosage. If it is clinically indicated to use a DRBD and there are no other alternative medications that could be used, it is important to avoid prolonged

treatment duration and high DRBD dosage.^{12,50,51} When used for the appropriate indication, physicians must be able to recognize the early symptoms and initiate appropriate management. When a patient develops TD, withdrawal of the offending drug should be the first management strategy as studies indicate worse morbidity and mortality in TD patients.^{52,53} One study looking at clinician attitudes in 3 countries found that although most psychiatrists inform their patients of the risk of developing TD before the initiation of a DRBD, most were also concerned about poor compliance due to awareness of side effects.⁵⁴ Some clinicians were concerned about causing unnecessary anxiety to their patients. In contrast, available evidence from several studies indicates that educational sessions about TD increase patient knowledge without a negative impact on compliance or clinical outcomes.⁵⁵⁻⁵⁷ Patients should be warned that TD often worsens transiently after DRBD withdrawal. If DRBD withdrawal alone fails, various pharmacological treatments may be considered.^{58,59}

In our opinion, tetrabenazine (TBZ) ameliorates TD most effectively, but access has been greatly limited in the United States pending FDA approval.⁶⁰ Both vitamin B₆⁶¹ and vitamin E⁶²⁻⁶⁷ have demonstrated a modest ability to improve TD in controlled studies. Case reports and case series offer other treatment options: donepezil,⁶⁸⁻⁷⁰ levetiracetam,⁷¹ and botulinum toxin.⁷² In extreme cases, surgical interventions with pallidotomy⁷³ and deep brain stimulation^{74,75} revealed promising results, but further studies are needed. Further investigations aimed to improve the treatment of TD are greatly needed.

In conclusion, this chart review of 434 TD patients indicates that over the past 25 years, haloperidol has been the most common etiologic agent causing TD, but referrals for metoclopramide-induced TD have increased dramatically. Unfortunately, the unique pharmacologic profile of metoclopramide leaves few alternative medications to treat certain medical issues—namely, gastroparesis. Patients treated with metoclopramide require close follow-up and careful examination for stereotypy, dystonia, and chorea as recommended by the American Psychiatric Association for patients treated with either first- or second-generation neuroleptics. The findings of this study may not be generalizable because of referral bias and its inherent weakness as a retrospective study of a single subspecialty clinic. More research is needed to develop medications that treat psychosis, tics, chorea, and gastroparesis through alternative pharmacologic mechanisms other than dopamine receptor antagonism.

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